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PHYSICO-CHEMICAL STUDY OF INDOLE ALKALOIDS MODELS [1]

V. STUDY OF THE STEREOCHEMISTRY OF QUINOLIZIDINE DERIVATIVES BY MEASUREMENT OF ASSOCIATION CONSTANTS WITH PHENOL AND 2,6-DIMETHYLPHENOL

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In order to study in a non destructive way the stereochemistry of nitrogen heterocyclic compounds related to natural products, we have measured the association constants between these bases and different proton donors. This method is well adapted to the problem because it can be adjusted to avoid the isomerisation by inversion of the nitrogen atom observed in certain cases by Shamma and Moss [3] during quaternisation studies of heteroyohimbine alkaloids.

Bellamy and co-workers [4], Dubois and Massat [5] and Gramstad [6] have already studied the influence of the intramolecular neighbourghood in the acceptor molecule on the H bond association in the carbonyl compounds - phenol and aliphatic tertiary amines - phenols systems.

Granstad showed clearly that it is possible to study steric hindrance in aliphatic tertiary amines by measurement of the association constant with a single proton donor.

He emphasized the fact that one has to distinguish between aliphatic tertiary amines and aza-aromatic bases with regard to their ability to form hydrogen bonds; the linear relationship found between the ln K_{ass} of the aza-aromatic bases with a single donor and the pKa values of these bases is not observed in the case of aliphatic tertiary amines. In this case, the corresponding points fall far away from a straight line what can be explained by steric hindrance at the nitrogen lone pair.

For these reasons we have undertaken the study of the association of phenol with very simple alkaloids models namely :

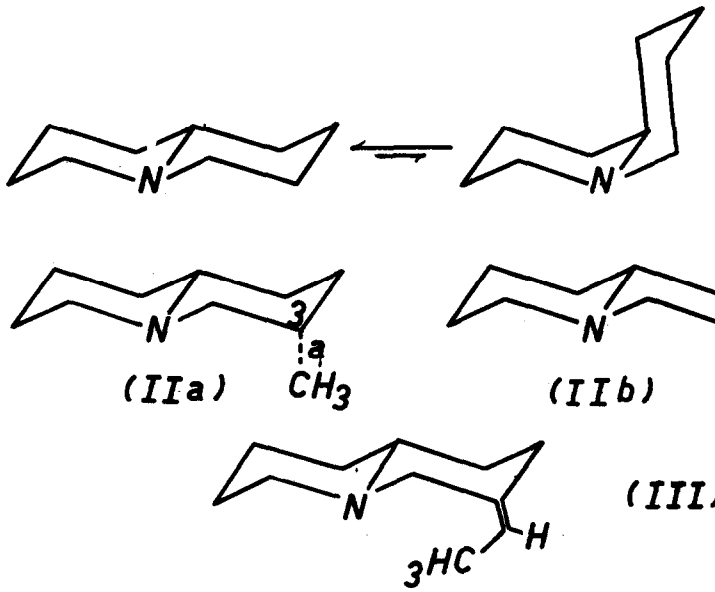
- quinolizidine (I)
- 3(a)-methylquinolizidine (IIa)
- 3(e)-methylquinolizidine (IIb)

in order to find a relationship between the stereochemistry in the neighbourghood of the nitrogen lone pair and the association constant. In this study we have also included the measurement of the association constant between phenol and 3-ethylidenequinolizidine (III) as there are many alkaloids with an ethylidene side chain β to the nitrogen atom.

Finally, to check our results, we have determined the association constant of quinolizidine with the 2,6-dimethylphenol known as an "hindered" phenol.

The preparation of the 3-ethylidenequinolizidine has never been reported so far. It was obtained in 80 % yield by condensation of triphenylethylphosphonium bromide on 3-quinolizidone using dimethylsulfoxide and sodium hydride according to Corey and Chaikowsky [7].

The methylquinolizidines were separated by gas liquid chromatography (Carbowax 20 M) and were used immediately because of their high instability to air. Each compound was checked by g.l.c. before use to ensure purity. Spectra were recorded on a Perkin Elmer 125 double beam grating spectrophotometer using 10 mm sodium chloride cells. The concentration of the solution used were in the range of 3 millimoles in donor to avoid self-association and in the range of 5 to 20 millimoles of acceptor.



The solvent used was tetrachlorethylene as it was almost impossible to record quantitative data in carbon tetrachloride because this solvent reacts very quickly with aliphatic amines to give their hydrochlorides [8].

The association constants were determined at 30° ± 1° by recording the height of the maximum of absorption of the phenol free ν OH band at 3613 cm^{-1} and using the relationship derived by Heinen [9]

$$K = \frac{A}{A_o - A} \cdot \frac{1}{[b]}$$

with A : absorbance of the phenol free ν OH band in the presence of base

[b] : concentration of base.

The results are given in the following table :

ASSOCIATION CONSTANTS OF VARIOUS QUINOLIZIDINE-PHENOL SYSTEMS.

DONOR	ACCEPTOR	$K_{ass}^{30°}$	pKa*
PHENOL	Quinolizidine (I)	36.5	8.3
	3(e)-methylquinolizidine (IIb)	33.2	8.5
	3(a)-methylquinolizidine (IIa)	11.9	8.8
	3-ethylidenequinolizidine (III)	33.8	8.3
2,6-DIMETHYL-PHENOL	Quinolizidine	6.5	

pKa* : determined in a dimethylcellosolve/water mixture 80:20

As shown, the variations of the pKa* values are all very small and are consistent with a minor polar effect rather than with steric hindrance [10]. However we observe a considerable lowering of the K_{ass} constants when an interaction occurs between a methyl group and the nitrogen lone pair in 1:3 diaxial position.

An effect of the same order of magnitude appears for the hindered phenol - acceptor pair (2,6-dimethylphenol/quinolizidine). In both cases, steric hindrance prevents the approach of the partenaires of the hydrogen bond.

On the other hand the introduction of an ethylidene side-chain in β to the nitrogen does not affect the equilibrium constant value as the accessibility of the nitrogen lone pair is not modified (though the conformation of one ring is altered).

In conclusion, measurement of association constants has so far proved to be a powerful and sensitive method to study steric hindrance in the acceptor as well as in the donor molecule, and we have shown that the introduction of an axial methyl group β to the nitrogen atom results in a considerable lowering of the hydrogen bond equilibrium constant.

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